Hepatic hypertrophic osteoarthropathy and liver transplantation

Hepatic hypertrophic osteoarthropathy (HOA) is a rare and disabling condition. It tends to respond poorly to conservative management such as analgesia or intra-articular injection of steroids. A recent article1 highlighted the benefits of successful liver transplantation in producing remission of this painful arthritis. We report a case of HOA which developed nine years after orthotopic liver transplantation (OLT).

A 44 year old man presented in February 1993 with three week history of pain and swelling of his wrists, knees and ankles. He had no previous arthritic symptoms. In 1979, he had developed primary sclerosing cholangitis and had undergone liver transplantation in 1985. A Roux-en-Y procedure was performed in 1991 for biliary stasis. Contrast cholangiography later that year demonstrated good biliary drainage. No strictures were present, but abnormal tapering of the distal biliary tree was noted. Because of continuing cholestasis, a liver biopsy was performed in September 1992. This showed chronic active hepatitis but no evidence of rejection. There was no recurrence of his original disease.

Examination revealed toe but not finger clubbing and he was markedly icteric. There was synovitis affecting the wrists, knees, and ankles, with tenderness proximal to the joints. Synovial fluid was non-inflammatory. Radiographs of the relevant joints showed a marked periosteal reaction consistent with HOA (figure). Chest radiograph was normal. The knee effusions responded to intra-articular steroid injection and the arthritis symptoms have resolved. However, his liver tests have continued to deteriorate slowly and repeat transplantation is being considered.

The pathogenesis of HOA is unknown. Hormonal, circulatory, and neurogenic factors have been implicated. It is thought that a growth factor mediated effect is probably involved2 leading to elevation of the periostea, new bone deposition and oedema of the surrounding tissues. This factor may accumulate as a result of impaired hepatic clearance or may be produced in excess by the liver as part of its response to disease. Hepatic HOA is rare.3 It is usually associated with cholestasis and is most commonly seen with primary biliary cirrhosis, chronic active hepatitis, and post-hepatic cirrhosis.

Liver transplantation, besides resulting in improved hepatic function, has also been shown to cause resolution of the joint symptoms of hepatic HOA.4 This may be because the stimulus for HOA, presumably resulting from the abnormal liver, has been removed. The syndrome can, however, recur novo after liver transplantation, in those with chronic rejection,5 or with recurrence of the underlying disease.

This patient has had two separate liver diseases. It is interesting that HOA did not occur in association with sclerosing cholangitis, but developed later with active inflammation in the grafted liver. While a minority of patients respond poorly to conservative management, this man’s symptoms resolved with intra-articular steroid administration and NSAIDs. If he undergoes repeat liver transplantation, it is possible that complete resolution of his HOA will be obtained.

Cytokine therapy in rheumatoid arthritis

The leader by Giles Campion has given a sure foundation on which to base our thoughts about cytokines, but is sparse on practical proposals.

For example, a recent Lancet article from Birmingham6 emphasised the early onset of osteoporosis in patients with rheumatoid arthritis (RA). We know that interleukins (IL) 1 and 6 and tumour necrosis factor α (TNFα) all play their part in causing osteoporosis,7 and the indications are that IL-1 receptor antagonist production is relatively poor in RA.8

Hence one application that will require trial in several different or combined centres will be the administration of IL-1 receptor antagonist, to see if osteoporosis is ameliorated.

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Author’s reply: The scarcity of practical proposals, as Dr Wardle puts it, was more a function of editorial space than editorial license.

In fact, a large multicentre trial of recombinant human interleukin-1 receptor antagonist (IL-1ra) in rheumatoid arthritis (RA) is currently in progress and much care is being taken to document potential effects of this therapeutic approach on bone. Support for the existence of such an effect comes from the observation that IL-1 stimulates bone resorption in vitro9 and in vivo10 and promotes the development of osteoclast precursors.11 IL-1 bioactivity is increased in peripheral blood monocytes during the menopause12 and a further increase is seen in high turnover osteoporosis.13 This effect may actually be regulated by the production of IL-1ra.14 As Dr Wardle mentions, production of IL-1ra has been shown to be deficient in the rheumatoid synovium,15 so the administration of this cytokine may be an appropriate means to reverse IL-1 pathology, including juxta-articular osteoporosis and erosions.

Whether antagonising one cytokine is enough remains to be seen. In the ovariectomized rat, bone loss during the first month occurs as a result of activation of the mature osteoclast, whereas during the second month, bone loss occurs after proliferation and differentiation of osteoclast precursors.16

Radiograph of the knees, demonstrating marked periostea reaction at the lower end of the femora.
Whereas IL-1ra can completely prevent the latter process, 2 blocking activation of the mature proinflammatory IL-1, requires simultaneous inhibition of TNF and IL-1. 3 It would therefore be logical to contemplate clinical trials in RA, inhibiting both of these cytokines and observing the effect on RA related osteoporosis as an end point.

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AUTHOR'S RESPONSE: DR Nikolov and his colleagues raise interesting questions. The three patients that they describe had a disease associated with severe pulmonary and vascular disease. However, as Nikolov et al imply, a key question is whether scleroderma and asthma may have a common pathogenic basis.

In addition to the observations offered in their letter, it is interesting that scleroderma and asthma do share certain pathogenic features; for example increased dermal mast cells and increased ability of mast cells to release histamine have been reported in scleroderma. Both these findings suggest that the pathogenesis of scleroderma may include a hypersensitive reaction similar to that described in asthma. 1 It is not clear if a similar process involving mast cells occurs in the lung in scleroderma, although circumstantial evidence suggests that it does.

Our report 2 suggested that scleroderma patients with centromere and histone antibody positive events of scleroderma and asthma, may have a more severe disease characterised by pulmonary and vascular involvement. It is not clear if the patients referred to by Nikolov et al had centromere antibodies, but both did have antibodies to histone H2A. Although review of our charts has not identified asthma as a clinical feature in our patients, based on the observations of Nikolov et al, future studies it may be important to determine if there are clinical correlations between the two diseases.

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LETTERS TO THE EDITOR

Ehlers Danlos syndrome and osteoporosis

Ehlers Danlos syndrome (EDS) is a group of inherited connective tissue disorders with extreme genetic and clinical variability. The clinical manifestations of EDS are a result of abnormalities in collagen types I and III, the main proteins of skin, ligament, tendons, blood vessels, and internal viscus. Type I collagen is also the main protein constituent of the bone matrix and its abnormalities form the molecular basis of osteogenesis imperfecta (OI). 10 EDS is therefore quite closely related to OI and the two conditions are known to coexist. 11 In spite of this there are no detailed studies available on bone mineral content in the Ehlers Danlos syndromes.

In the past three years we have seen seven patients with EDS and assessed bone densities in the lumbar spine and hip using dual energy x-ray absorptiometry. A 65 year old lady referred from the orthopaedic department for investigations of a wedge fracture of the L2 vertebra. She did not have any obvious precipitating causes for osteoporosis in her past medical, menstrual,